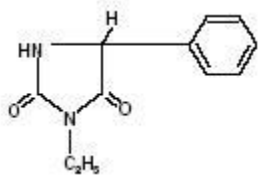
PEGANONE - ethotoin tablet
Lundbeck Inc.

DESCRIPTION

PEGANONE (ethotoin tablets, USP) is an oral antiepileptic of the hydantoin series and is chemically identified as 3-ethyl-5-phenyl-2,4-imidazolidinedione. It is represented by the following structural formula:



PEGANONE tablets are available in a dosage strength of 250 mg.
Inactive Ingredients: Acacia, lactose, sodium carboxymethylcellulose, stearic acid and talc.

CLINICAL PHARMACOLOGY

PEGANONE (ethotoin tablets, USP) exerts an antiepileptic effect without causing general central nervous system depression. The mechanism of action is probably very similar to that of phenytoin. The latter drug appears to stabilize rather than to raise the normal seizure threshold, and to prevent the spread of seizure activity rather than to abolish the primary focus of seizure discharges.
Ethotoin is fairly rapidly absorbed; the extent of oral absorption is not known. The drug exhibits saturable metabolism with respect to the formation of N-deethyl and p-hydroxyl-ethotoin, the major metabolites. Where plasma concentrations are below about 8 µg/mL, the elimination half-life of ethotoin is in the range of 3 to 9 hours. A study comparing single doses of 500 mg, 1000 mg, and 1500 mg of PEGANONE (ethotoin tablets, USP) demonstrated that ethotoin, and to a lesser extent 5-phenylhydantoin, a major metabolite, exhibits substantial nonlinear kinetics. The degree of nonlinearity with multiple dosing may be increased over that seen after a single dose, given the likelihood of plasma accumulation based on a reported elimination half-life of 6 to 9 hours and a dosing interval of 4 to 6 hours. Experience suggests that therapeutic plasma concentrations fall in the range of 15 to 50 µg/mL; however, this range is not as extensively documented as those quoted for other antiepileptics.
In laboratory animals, the drug was found effective against electroshock convulsions, and to a lesser extent, against complex partial (psychomotor) and pentylenetetrazol-induced seizures. In mice, the duration of antiepileptic activity was prolonged by hepatic injury but not by bilateral nephrectomy; the drug is apparently biotransformed by the liver.

INDICATIONS AND USAGE

PEGANONE (ethotoin tablets, USP) is indicated for the control of tonic-clonic (grand mal) and complex partial (psychomotor) seizures.

CONTRAINDICATIONS

PEGANONE (ethotoin tablets, USP) is contraindicated in patients with hepatic abnormalities or hematologic disorders.

WARNINGS

Suicidal Behavior and Ideation:
Antiepileptic drugs (AEDs), including PEGANONE, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.
The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.
The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table1: Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.
Anyone considering prescribing PEGANONE or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Use in Pregnancy:
Peganone (ethotoin tablets, USP) can cause fetal harm when administered to a pregnant woman. There are multiple reports in the clinical literature which indicate that the use of antiepileptic drugs during pregnancy results in an increased incidence of birth defects in the offspring. Although data are more extensive with respect to phenytoin and phenobarbital, reports indicate a possible similar association with the use of other antiepileptic drugs. Therefore, antiepileptic drugs should be administered to women of child-bearing potential only if they are clearly shown to be essential in the management of their seizures.
Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both mother and the unborn child. Consideration should, however, be given to discontinuation of antiepileptics prior to and during pregnancy when the nature, frequency and severity of the seizures do not pose a serious threat to the patient. It is not, however, known whether even minor seizures constitute some risk to the developing embryo or fetus.
Reports have suggested that the maternal ingestion of antiepileptic drugs, particularly barbiturates, is associated with a neonatal coagulation defect that may cause bleeding during the early (usually within 24 hours of birth) neonatal period. The possibility of the occurrence of this defect with the use of PEGANONE should be kept in mind. The defect is characterized by decreased levels of vitamin k-dependent clotting factors, and prolongation of either the prothrombin time or the partial thromboplastin time, or both. It has been suggested that vitamin k be given prophylactically to the mother one month prior to and during delivery, and the infant, intravenously, immediately after birth.
If PEGANONE is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
To provide information regarding the effects of *in utero* exposure to PEGANONE, physicians are advised to recommend that pregnant patients taking PEGANONE enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll- free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

PRECAUTIONS

General:
Blood dyscrasias have been reported in patients receiving PEGANONE. Although the etiologic role of PEGANONE has not been definitely established, physicians should be alert for general malaise, sore throat and other symptoms indicative of possible blood dyscrasia.
There is some evidence suggesting that hydantoin-like compounds may interfere with folic acid metabolism, precipitating a megaloblastic anemia. If this should occur during gestation, folic acid therapy should be considered.

Information for Patients:
Patients should be advised to report immediately such signs and symptoms as sore throat, fever, malaise, easy bruising, petechiae, epistaxis, skin rash or others that may be indicative of an infection or bleeding tendency.

Patients, their caregivers, and families should be counseled that AEDs, including PEGANONE, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers.
Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 (**see Use In Pregnancy**).

Laboratory Tests:
Liver function tests should be performed if clinical evidence suggests the possibility of hepatic dysfunction. Signs of liver damage are an indication for withdrawal of the drug.
It is recommended that blood counts and urinalyses be performed when therapy is begun and at monthly intervals for several months thereafter. As in patients receiving other hydantoin compounds and other antiepileptic drugs, blood dyscrasias have been reported in patients receiving PEGANONE (ethotoin tablets, USP). Marked depression of the blood count is indication for withdrawal of the drug.

Drug Interactions:
PEGANONE used in combination with other drugs known to adversely affect the hematopoietic system should be avoided if possible.
A two-way interaction between the hydantoin antiepileptic, phenytoin, and the coumarin anticoagulants has been suggested. Presumably, phenytoin acts as a stimulator of coumarin metabolism and has been reported to cause decreased serum levels of the coumarin anticoagulants and increased prothrombin-proconvertin concentrations. Conversely, the coumarin anticoagulants have been reported to increase the serum levels and prolong the serum half-life of phenytoin by inhibiting its metabolism. Although there is no documentation of such, a similar interaction between ethotoin and the coumarin anticoagulants may occur. Caution is therefore advised when administering PEGANONE to patients receiving coumarin anticoagulants.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No data are available on long-term potential for carcinogenicity in animals or humans.

Pregnancy:
Pregnancy Category D. See "**WARNINGS**" section.

Nonteratogenic Effects:
Reports have suggested that the maternal ingestion of antiepileptic drugs, particularly barbiturates, is associated with a neonatal coagulation defect that may cause bleeding during the early (usually within 24 hours of birth) neonatal period. The possibility of the occurrence of this defect with the use of PEGANONE should be kept in mind. See "**WARNINGS**" section.

Nursing Mothers:
Ethotoin is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from ethotoin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in the pediatric population were established on the basis of open-label, uncontrolled experience in patients down to the age of one with various types of seizures.

Geriatric Use:
Clinical studies of PEGANONE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Adverse reactions associated with PEGANONE, in decreasing order of severity, are:
Isolated cases of lymphadenopathy and systemic lupus erythematosus have been reported in patients taking hydantoin compounds, and lymphadenopathy has occurred with PEGANONE. Withdrawal of therapy has resulted in remission of the clinical and pathological findings. Therefore, if a lymphoma-like syndrome develops, the drug should be withdrawn and the patient should be closely observed for regression of signs and symptoms before treatment is resumed.
Ataxia and gum hypertrophy have occurred only rarely—usually only in patients receiving an additional hydantoin derivative. It is of interest to note that ataxia and gum hypertrophy have subsided in patients receiving other hydantoins when PEGANONE (ethotoin tablets, USP) was given as a substitute antiepileptic.

Occasionally, vomiting or nausea after ingestion of PEGANONE has been reported, but if the drug is administered after meals, the incidence of gastric distress is reduced. Other side effects have included chest pain, nystagmus, diplopia, fever, dizziness, diarrhea, headache, insomnia, fatigue, numbness, skin rash, and Stevens-Johnson syndrome.

OVERDOSAGE

Symptoms of acute overdosage include drowsiness, visual disturbance, nausea and ataxia. Coma is possible at very high dosage. Treatment should be begun by inducing emesis; gastric lavage may be considered as an alternative. General supportive measures will be necessary. A careful evaluation of blood-forming organs should be made following recovery.

DOSAGE AND ADMINISTRATION

PEGANONE (ethotoin tablets, USP) is administered orally in 4 to 6 divided doses daily. The drug should be taken after food, and doses should be spaced as evenly as practicable. Initial dosage should be conservative. For adults, the initial daily dose should be 1 g or less, with subsequent gradual dosage increases over a period of several days. The optimum dosage must be determined on the basis of individual response. The usual adult maintenance dose is 2 to 3 g daily. Less than 2 g daily has been found ineffective in most adults.

Pediatric dosage depends upon the age and weight of the patient. The initial dose should not exceed 750 mg daily. The usual maintenance dose in children ranges from 500 mg to 1 g daily, although occasionally 2 or (rarely) 3 g daily may be necessary.

If a patient is receiving another antiepileptic drug, it should not be discontinued when PEGANONE therapy is begun. The dosage of the other drug should be reduced gradually as that of PEGANONE is increased. PEGANONE may eventually replace the other drug or the optimal dosage of both antiepileptics may be established.

In tonic-clonic (grand mal) seizures, use of the drug with phenobarbital may be beneficial.

HOW SUPPLIED

PEGANONE (ethotoin tablets, USP) 250 mg grooved, white tablets bearing the letters OV on one side and the number 61 on the other and are supplied in bottles of 100 (NDC 67386-601-01).

Recommended storage: Store below 77°F (25°C). Dispense in a tight light-resistant container, as defined in the USP, with a child-resistant cap.

Manufactured by: Abbott Laboratories
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For:
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